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THE ROCKEFELLER UNIVERSITY

RESEARCH PROFILES

SPRING 1990

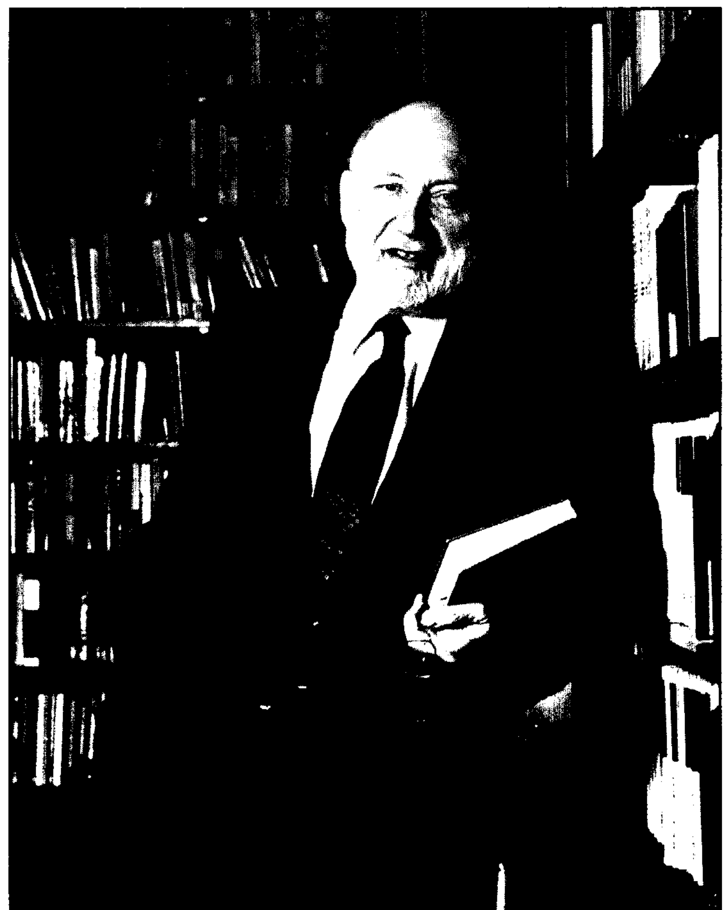
"Every creative act involves...a new innocence of perception, liberated from the cataract of accepted belief."

ARTHUR KOESTLER
The Sleepwalkers

"There is no end to our searchings... No generous mind stops within itself. Its pursuits are without limit; its food is wonder, the chase, ambiguity."

MONTAIGNE (1533-1592)

Report on the President



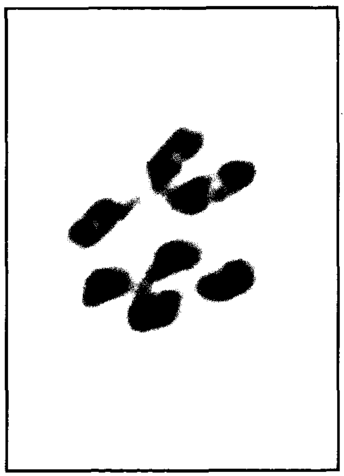
Joshua Lederberg

For more than forty years, Joshua Lederberg has rarely been far from the center of scientific activity and debate. In 1946, at the age of twenty-one, he burst upon the biological world with the announcement that bacteria have a sex life. In 1958, he was awarded a Nobel Prize (at the age of 33) for his studies of organization and recombination of genes in bacteria.

Possessed of an intellectual appetite that has been described as "omnivorous," and a penchant for questioning the common wisdom, his speculations have propelled him, at various times, into outer space (figuratively speaking), into the "brains" of computers, and into the councils of government and industry.

Before his 1978 appointment as president of The Rockefeller University, Lederberg led distinguished genetics departments at the University of Wisconsin and the Stanford University School of Medicine. His pioneering research into the molecular mechanism of genes and their application in recombinant DNA technology today informs virtually every field of biology and promises to revolutionize medical diagnosis and treatment.

Transmission of genetic information between two E. coli *bacteria occurs during a process known as conjugation. Dr. Lederberg discovered this process in 1946, proving that a form of sexual reproduction occurs in these asexual microorganisms. In the micrograph below, two bacteria make cell-to-cell contact through the formation of a connecting bridge. The bacterium acting as a male donor contributes DNA to the bacterium acting as a female recipient. The recipient incorporates the new genetic information into its own chromosome by recombination and passes the recombined set on to its progeny by replication.*



THE "LONG-SHOT" EXPERIMENT

Joshua Lederberg was a pre-medical student at Columbia University in 1944 at the time of the first experimental evidence that DNA—deoxyribonucleic acid was the genetic material, at least in bacteria. This work was published by Oswald Avery, Colin MacLeod, and Maclyn McCarty, scientists working at the research hospital of The Rockefeller Institute for Medical Research (later The Rockefeller University).

Some years earlier, it had been observed that non-virulent strains of pneumonia bacteria became infectious when mixed with heat-killed, infectious strains. Painstaking investigation of this puzzling phenomenon revealed to Avery and his team that the non-infectious bacteria picked up loose threads of DNA that had been released from their once-lethal neighbors, and that the acquired DNA and its power of infectivity were retained in the progeny of the transformed bacteria.

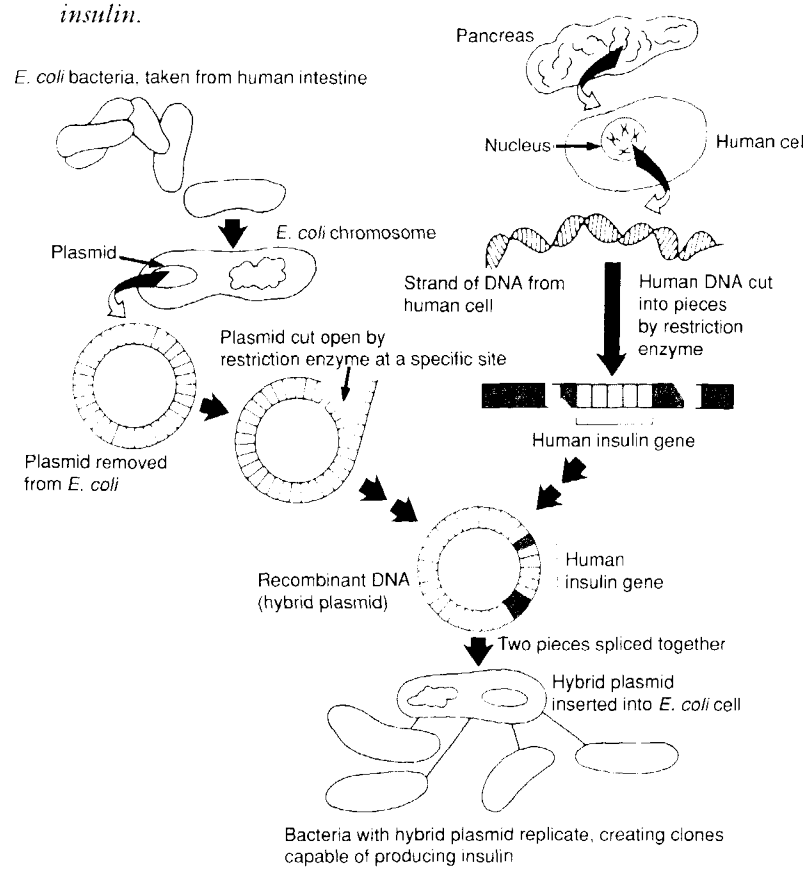
A medical degree was then considered the proper route to the goal of biomedical research, but Lederberg spent most of his time in the laboratory of geneticist Francis Ryan, where the Rockefeller discovery caused a considerable stir. As Lederberg later wrote: "When biologists of that era used terms like protein, nucleic acid, or nucleoprotein, it can hardly be assumed that the words had today's crisp connotations of defined chemical structure. Sleepwalking, we were all groping to discover just what was important about the chemical basis of biological specificity. It was clear to the circle I frequented at Columbia that Avery's work was the most exciting key to that insight."

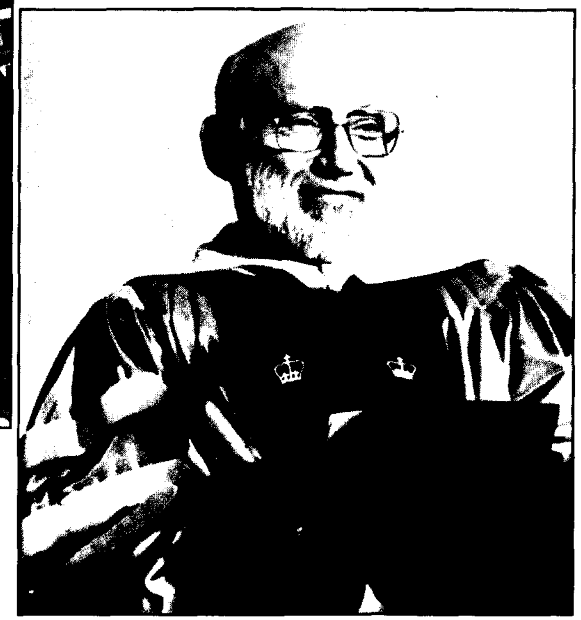
The inspired young medical student deliberated on how to "advance these new hints about the chemistry of the gene" and the genetics of bacteria. It had been assumed that bacteria always reproduce simply by dividing into two genetically identical daughter cells, making comparative analysis impossible. However, since there were other microorganisms known to have a sexual stage, a few microbiologists had pondered the possibility in bacteria. It seemed clear to Lederberg that

Gene Genies:

In addition to a main chromosome, bacteria contain plasmids—small, circular molecules of double-stranded DNA which replicate autonomously. Scientists are able to insert foreign DNA into plasmids, which then multiply and produce cells containing genetically identical material, or clones.

To introduce a human gene (in this case, the one for insulin) into a plasmid, scientists take the plasmid out of an E. coli *bacterium, break the plasmid open at a specific site by means of a restriction enzyme, and splice in insulin-making human DNA. The resulting hybrid plasmid can be inserted into another* E. coli *bacterium, where it replicates together with the bacterium, making it capable of producing large quantities of insulin.*





Lederberg Through the Years: (l. to. r.) Joshua Lederberg as a pre-med student, 1945; at the University of Wisconsin, 1958; at Stanford University, circa 1960; installed as president of The Rockefeller University, 1978.

"questions about the biological significance of transformation in bacteria (i.e. Avery's finding) would continue to fester so long as bacteria remained inaccessible to conventional genetic analysis for lack of a sexual stage."

Francis Ryan had done postdoctoral research at Stanford University with George Beadle and Edward Tatum who would later share a Nobel Prize (awarded the same year as Joshua Lederberg's) for their discovery that genes control chemical reactions through the proteins called enzymes. Tatum had recently moved his laboratory to Yale, where he was developing a mutant strain of a common bacterium, *E. coli*, which Lederberg believed might be a suitable model for research on sexual behavior. With Ryan's encouragement and Tatum's agreement, Lederberg took what he thought would be a short break from his medical studies to go to Tatum's lab in March 1946 and try what he termed a "long-shot" experiment.

It succeeded beyond his "wildest expectations." Within a few weeks he had uncovered a system whereby two bacteria attach and form a connecting bridge through which one passes a chromosomal strand to the other. The discovery of this mechanism, called conjugation, helped to confirm the existence of bacterial genes and made bacteria available for genetic research.

PLASMIDS AND RECOMBINANT DNA TECHNOLOGY

Lederberg never returned to medical school. After earning a Ph.D. with Tatum in 1947 he received an appointment at the University of Wisconsin, where for the next dozen years, he and his colleagues continued to explore the ramifications of bacterial recombinations.

Recombinant DNA technology exploits the capacity of bacteria to carry extra rings of genetic material, called plasmids (a term coined by Dr. Lederberg), outside of their chromosomes. In gene cloning, a plasmid is removed from a bacterium, cut open with enzymatic "scissors," and a segment of foreign DNA (for example, the gene for human insulin) is spliced into the plasmid ring. The recombinant plasmid is then closed up and returned to the bacterium, which proceeds to churn out daughter cells containing the inserted gene.

The development of recombinant DNA technology derived from scientists' observations of natural recombinant mechanisms in bacteria. This involved the crossing over of independent genetic combinations through transformation, through conjugation, and most analogously, through transduction, a process discovered by Rockefeller Professor Norton Zinder while he was a graduate student in Dr. Lederberg's Wisconsin laboratory.

Like other organisms, bacteria are subject to infection by viruses. The viruses that attack bacteria are called bacteriophages, or phages for short. What Dr. Zinder learned was that bacteriophages can pick up genes from one bacterium and move them to another. "It was an exciting time," Dr. Lederberg says. "We were exploring a completely new territory that we only dimly understood. We weren't looking for transduction—we bumped into it. We weren't looking for plasmids—we bumped into them. Every time we turned around we found something unexpected."

PLANET PROBES

Other kinds of excitement were to come when Dr. Lederberg spent a few months in Australia as a Fulbright Visiting

With new discoveries and concepts come the need for new names. Here are some words coined by Joshua Lederberg, both alone and in conjunction with his research colleagues, as they appear in the Oxford English Dictionary.

exo- ('ɛksəʊ; before two unstressed syllables ɛk'sɒ). *prefix*[1] (before a vowel sometimes reduced to *ex-*), repr. Gr. ἔξω, without, in many compounds of modern formation, as **exarte'ritis**, **,exo-arte'ritis** [see ARTERITIS], *Path.*, inflammation of the outer coat of an artery; **exoatmos'pheric** *a.*, occurring or working outside the atmosphere; **exobi'ology** **(see quot. 1960); hence exobi'ologist;**

1966 *Economist* 5 Mar. 898/1 A 'new, long-range *exoatmospheric interceptor' to which the short-range Sprint missile would be a supplement. **1967** *Listener* 9 Feb. 185/2 The resulting pulse of radiation should make almost everything in range boil; this would happen beyond the atmosphere and the principle is called exoatmospheric interception. **1964** *New Scientist* 26 Nov. 573/2 One of the greatest difficulties the *exobiologists are up against is that of making sure that their equipment does not carry any extraneous terrestrial bacteria. **1969** *New Yorker* 12 Apr. 85/1 Exobiologists will be looking for traces of life on the moon. **1960** ***Daily Tel.*** **14 Jan. 11/1 Dr. Lederberg is building up a team for work on *exobiology, as this branch of the study of life on other planets is called.** **1960** *Space Research* I. 1153 The problems of exobiology have important applications for the development of theoretical biology and the understanding of the mechanism of the evolution of life

plasmid ('plæzmɪd). *Biol.* [f. PLASM + *-id* (cf. ID, CHROMATID).] Any genetic structure in a cell that can replicate independently of the chromosomes; *esp.* one in the cytoplasm of a bacterium.

1952 J. Lederberg in *Physiol. Rev.* XXXII. 403, I propose *plasmid* as a generic term for any extrachromosomal hereditary determinant. *Ibid.*, The taxonomic classification of plasmids as viruses, symbionts, or plasmagenes should not obscure careful descriptions of their function, hereditary or pathological, or both. *Ibid.* 414, κ, a plasmid in *Paramecium aurelia*. *Ibid.* 425 This review has contrasted the various forms of plasmid: the hereditary parasites as ...ctionally coordinated plasmagenes, with the ...ndosymbionts somewhere between.

transduction (trɑːns'dʌkʃən, træns-). [ad. L. *transduction-em* (usually *trāductiōnem*), n. of action f. *tra(ns)dūcĕre*: see TRADUCE.]

1. The action of leading or bringing across. *rare.*

1656 Blount *Glossogr.*, *Transduction*, a leading over, removing from one place to another. *a* **1816** Bentham *Offi. Apt. Maximized, Introd. View* (1830) 19 In lieu of *adduction* as the purpose requires, will be subjoined *abduction, transduction*,...and so forth.

2. The action or process of transducing a signal.

1947 *Jrnl. Acoustical Soc. Amer.* XIX. 307/1 It is rather interesting that the direct method of electronic transduction, instead of the indirect method of employing a conventional transducer and then amplifying the output with a vacuum tube, has not been developed. **1970** J. Earl *Tuners & Amplifiers* iv. 87 Low impedance pickup cartridges...using the moving-coil principle of transduction. **1975** *Nature* 17 Apr. 625/1 The transduction of light energy into neural signals is mediated in all known visual systems by a common type of visual pigment.

3. *Microbiology.* The transfer of genetic material from one cell to another by a virus or virus-like particle.

1952 Zinder & Lederberg in *Jrnl. Bacteriol.* LXIV. 681 To help the further exposition of our experiments, we shall use the term transduction for genetically unilateral transfer in contrast to the union of equivalent elements in fertilization. **1960** [see F III. 1]. **1971** *Nature* 18 June 466/1 It has been suggested that transduction of genes by viruses was an important mechanism in evolution for spreading useful mutations between organisms not formally related.

prototroph ('prəʊtəʊtrəʊf, -trɒf). *Genetics.* [f. as next.] A strain (usu. of bacteria or fungi) which can grow on the simplest medium necessary for the growth of its species, without supplementary nutrients.

1946 Ryan & Lederberg in *Proc. Nat. Acad. Sci.* XXXII. 172 We propose to designate as a prototroph any strain which has the nutritional requirements of the 'wild type' from which it was derived irrespective of how it became prototrophic. **1952** *Genetics* XXXVII. 720 The occurrence of prototrophs, thus selected, from platings of thoroughly investigated auxotroph parents has been taken as *prima facie* evidence of crossing

euphenics (juː'fɛnɪks). *Biol.* [f. Gr. εὐ- EU- + φαίν-ειν to show, appear + -ICS.] A practice analogous to eugenics in which physical improvement of man is sought through the modification and control of his development (as by chemical or surgical means).

1963 J. Lederberg in *Nature* 4 May 428/2, I propose the term 'euphenics' as the counterpart of 'eugenics', in the same sense that 'phenotype' is opposed to 'genotype'. **1965** *New Scientist* 9 Dec. 714/2 By 'cultural euphenics'...one could make revolutionary changes in a generation. **1967** *Technology Week* 23 Jan. 50/3 Euphenics [is] the modification of his [*sc.* man's] biological development.

Joshua Lederberg receiving the Presidential Medal of Honor from George Bush, 1989.

Professor in the University of Melbourne laboratory of immunologist Sir MacFarlane Burnet. He participated in research on antibody production that would earn Burnet a Nobel Prize in 1960, and he witnessed the ascent of Sputnik in the southern skies on October 4, 1957, an event that filled him with both awe and apprehension. On returning to his own laboratory, he read extensively on astronomy and rocketry and, by December, he had sent off memos to several influential scientists asking their help to avert what he saw as a potential "cosmic catastrophe": the contamination of life forms that might be present on other planets by organisms carried from earth via space flight.

"I was the only biologist at that time who seemed to take the idea of extraterrestrial exploration seriously," he remarks. "People were saying it would be a hundred years before we even got to the moon." Combined with his deep respect for evolutionary inventiveness, he was probably also the only biologist who had just steeped himself in space technology. "I was convinced," he says, "that once the first satellite was up the timetable would be very short, and my fear was that the space program would be pushed ahead for military and political reasons without regard for the scientific implications."

Among those to whom he had written and who paid heed to his warnings were Detlev Bronk and Frederick Seitz, officers of the National Academy of Sciences (who, coincidentally, served successively as presidents of The Rockefeller University, preceding Dr. Lederberg). By February 1958, the Academy's council had expressed formal concern, and an international committee was formed to establish guidelines and plan methods for detecting and protecting life in space.

Dr. Lederberg served on the Academy's committees on space biology from 1958 to 1977, and on NASA's lunar and planetary missions boards, involved with the Mariner and Viking missions, from 1960 to 1977.

THE STANFORD YEARS

Sociologist Harriet Zuckerman, author of *Scientific Elite*, a study of American Nobel Laureates, characterizes her longtime friend Joshua Lederberg (one of the subjects of her book and a sometimes collaborator in studies of the history and sociology of science), as a man whose interests are "deep and diverse enough for several life histories."

During his Stanford years, from 1959 to 1978, his academic titles included professor and chairman of genetics, professor of biology, and professor of computer science. His extracurricular activities, in addition to participation in the space program, included membership in nine or ten governmental and scientific agencies and commissions, including panels of the President's Science Advisory Committee. He served on President John F. Kennedy's Panel on Mental Retardation and directed research on the genetics, development, and neurobiology of retardation at the Kennedy Laboratories for Molecular Medicine at Stanford.

His appointment to Stanford's medical school faculty gave him the opportunity he had been wanting: to relate genetics to the wider context of human health and biology, particularly neurobiology and mental illness—subjects that had interested him since childhood. As chairman of genetics, he oversaw a large and diverse research group. He also helped institute a human biology curriculum for undergraduates.

His involvement with the space program had introduced him to the potential of computers for data analysis and problem solving, which he wanted to apply to biology. He formed a collaboration with Edward Feigenbaum, chairman of computer science at Stanford. With the participation of another computer scientist, Professor Bruce Buchanan and, later, Carl Djerassi, a professor of chemistry, they created DENDRAL, a computer program to generate structures of organic molecules and to explore how molecules exist in nature. It became the prototype for all so-called expert systems. They followed DENDRAL with a program for experiment design and data analysis in molecular genetics, and a computerized consultant in infectious diseases. In 1974, with support from the National Institutes of Health, they established SUMEX, the Stanford University Medical Experimental Computer, to provide hardware for research projects all over the country.

In 1966, deciding that there was a need for increased public awareness and understanding of science, he initiated and wrote a weekly column for *The Washington Post,* in which, over a period of six years, he commented on everything from manipulating genes to manipulating weather, science ethics, science education, the environment, the history of medicine, and the state of science reporting itself.

AS UNIVERSITY PRESIDENT

The move to New York brought Dr. Lederberg back to the city where he grew up and where his distinctive style of debate was honed in "quasi-Talmudic argumentation" with his rabbi father. His precocity was apparent early—he asked questions his teachers couldn't answer. His hunger for science was fed in the library. If there were, as he says, no "dark clouds" in his childhood, he does remember being "very lonely" for someone to share his interests, a problem that was resolved upon his admission to Stuyvesant High School, one of the city's renowned training grounds for budding Nobelists. Like many of New York's children of immigrant parents, his passage to higher education was made on scholarships, the subway, and the New York Public Library.

The venerable New York City institution he returned to preside over had undergone some changes since Oswald Avery's day. The 1950s and 1960s had brought physical expansion to the campus and the establishment of a graduate degree program. His own thinking, however, coincided with what the board of trustees had been deciding: there was a need to re-emphasize the university's traditional strengths.

Almost all of the new laboratories that have been established during Dr. Lederberg's administration concentrate on biomedical investigations and lean heavily on the insights and methods of molecular biology. Their leaders have been recruited from across the country and the world, as well as from the university's own ranks. While the Rockefeller retains its long-standing commitment to basic research in the biological and physical sciences, the new groups have expanded the university's thrust in such areas as heart disease, cancer, mental and neurological illness, and infectious diseases, including diseases of the Third World.

Building new laboratories and renovating old ones, not to mention trying to resolve the problem of attracting promising young investigators to a city of astronomical housing costs, has required a lot of planning, revenue management, and fund-raising. This past fall a new university apartment building, Scholars Residence, opened next to the existing Faculty House. A superb new laboratory building is currently under construction, part of which will house scientists who share joint appointments on the Rockefeller faculty and as investigators in a unit of the Howard Hughes Medical Institute, which was established at the university during Dr. Lederberg's tenure.

THE FUTURE

Dr. Lederberg received the National Medal of Science, the nation's highest scientific award, this past October. Now, after twelve years, he reaches mandatory retirement age as president this coming July 1 and returns to research as a professor at the Rockefeller. He plans to continue lab work and the study of theory formation in molecular genetics. He also plans to maintain his participation in public activities, particularly in international arms control as a member of the NAS Committee on International Security and Arms Control. He is deeply concerned about the threats to humanity from naturally emerging viruses. In addition, as co-chairman of the Carnegie Corporation's blue-ribbon commission, he will assess and advise the federal and state governments on issues of science and technology. As a voluntary adjunct professor at his alma mater, Columbia University, he will again counsel undergraduate students on their research interests in the broad fields of science in which he has knowledge.

A busy agenda, he admits, adding that the allure of bench research is still quite strong. "There are still some elementary but important tasks left undone in bacterial genetics," he says.

RESEARCH PROFILES is published four times a year by The Rockefeller University. This issue was written by Judith N. Schwartz. Inquiries should be addressed to the University's Public Information Office, 1230 York Avenue, New York 10021; or phone (212) 570-8967. Photograph: Page 1: Ingbet Grüttner. Micrograph: Page 2: courtesy of Dr. Joshua Lederberg, The Rockefeller University. Photographs: Page 3: (l. to r.) courtesy of Nature Magazine; courtesy of Dr. Joshua Lederberg, The Rockefeller University; courtesy of Stanford University; courtesy of the Rockefeller Archive Center. Photograph: Page 5: courtesy of Dr. Joshua Lederberg, The Rockefeller University. Illustration by Dennis Stillwell. Design by the Stillwell Group, NYC.